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PRINCIPAL INVESTIGATOR: Xiaoli Yu, Ph.D.

CONTRACTING ORGANIZATION: The University of Southern California
Los Angeles, California 90089-9074

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Xiaoli Yu, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The University of Southern California
Los Angeles, California 90089-9074

E-Mail: xiyu@csi.usc.edu

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13. ABSTRACT (Maximum 200 Words)

The goal of this project is to improve the detection of metastatic axillary breast cancer through sophisticated physiological modeling and statistical signal processing techniques. The major focus of Year 4 (no-cost extension) was the assessment of the developed methodology in feature identification, extraction/estimation, and early detection with digital phantom, animal study and a small amount of patient data. The methods we tested include (i) adding the factor analysis to the conventional ROI averaging method for feature extraction/estimation and (ii) to develop the optimal feature-guided filtering criteria for early lesion detection. The objective is to suppress the interference-plus-noise in dynamic data proceeding to applying the hypothesis test detection criteria. Two types of filters presented in the last annual report, with/without using the physiological features extracted from normal tissues, were further tested with digital phantom, animal study and patient data. The results of phantom study demonstrated that the accuracy of feature extraction in the modified method can be dramatically improved compared to the conventional ROI analysis and that the feature-guided space-temporal filters can enhance the SNR in invisible lesion and make it become detectable. The assessment of non-invasive blood time activity extraction was also performed with patient data selected from our clinical database. All findings in theory and simulations will be continued in the extended year 5 when more clinical data will become available.

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1. Introduction

The whole proposed study consists of four tasks: *Task 1*: Developing the mathematical formula to linearly map and identify the physiological features contained in PET dynamic sinogram sequence (Month 1-8), *Task 2*: Developing the schemes for objective reduction of dynamic sinogram data guided by the identified TAC subspaces of the desired signal (tumor) and the interference (normal tissue background plus noise) (Month 4 - 12), *Task 3*: Deriving and analyzing statistical hypothesis test criteria to test the presence of an axillary metastasis in the dynamic images reconstructed from the compressed sinogram data (Month 13 - 24), and *Task 4*: Clinical Evaluation (Month 13 - 36). For each task, several subtasks were defined (see the SOW in the grant application for details).

2. Body

The three year grant was originally funded until July 31, 2002. However, after the first year's annual report, it was brought to our attention that we needed to obtain approval from the U.S. Army Medical Research and Material Command Institutional Review Board (US Army IRB). Although patients whose data are used in this study will have a PET scan regardless of their participation in this study, they still must be prospectively recruited for "additional" (temporal-based) images. Since November 2000 the Army IRB had have a hold on the acquisition of the clinical data under this grant till May 2002; therefore, we have not obtained all of the data needed to complete the funded objectives.

We have requested a 12 month no-cost extension of the funding period for this project. As the US Army Medical Research Command is well aware of the delays with the clinical data, the request was proved. But due to a new PET/CT scanner purchased at the USC PET Clinical Center, the old PET scanner which has the capability to acquire dynamic scans had to be moved to and installed at our research facility, thus the completion of patient data acquisition and analysis for this project has been further delayed.

Although the research efforts have been still mainly limited to analyses of dynamic imaging data that already existed in the patient database of USC PET center as well as phantom data, progresses have been continually made through this year via phantom study, animal study as well as a small amount of patient study. The major accomplishments of this activity are presented as follows:

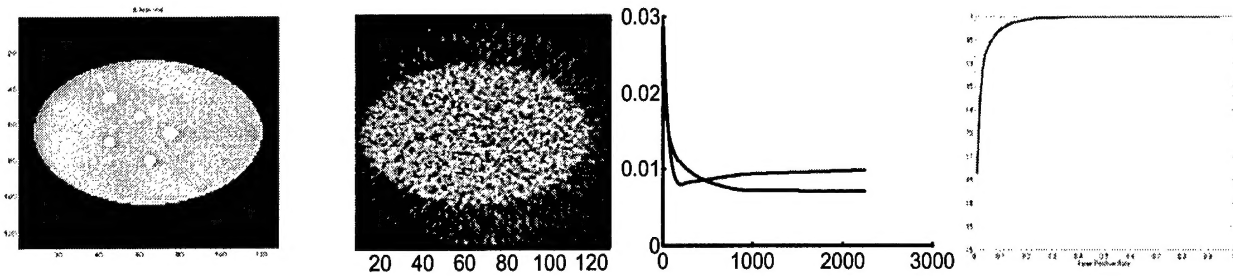
2.1 Assessment of the developed methods with digital phantom

Digital phantom study:

The image of the digital phantom is shown in Figure 1 (a). There are five lesions in the ellipse. The lesions were assigned with the time activity curve collected in a proven lung metastatic malignant and the rest of the ellipse was assigned with the time activity curve in lung normal tissues, respectively. These curves are shown in Figure 1 (c). By forward projecting, the dynamic phantom sinogram data were generated and certain amount of Poisson noise was added to the projections. The noise energy level was controlled to make the lesions invisible in all the frames of FBP reconstructed images. The last frame FBP reconstructed image is presented in Figure 1 (b). None of the five lesions can be visualized as desired.

Assuming that the time activity curves in the lesions and the background are known in prior, we tested at each pixel whether the time activity curve observed is more similar to the lesion TAC or the

background TAC in the sense of mean square errors. If at a pixel, the TAC observation is closer to the lesion TAC, then a lesion is detected at that pixel. Otherwise, the pixel is declared to be a normal tissue. 50 sets of dynamic phantom data were generated with/without adding digital lesions for a ROC study. The resulted ROC is given in Figure 1 (d). Although in reality the feature knowledge we know about lesion and normal tissues is not exactly the same as those in faint or invisible metastases, the resulting ROC demonstrates the potential to improve early metastasis detection from almost zero to 10% - 20%.



(a) (b) (c) (d)

Figure 1: (a) Digital phantom image; (b) FBP reconstructed image of (a); (c) Time activity curves assigned to lesions (red) and background (blue); (d) The measured ROC curve

2.2 Assessment of the developed methods with animal study

We evaluated the proposed methods for early detection in vivo using animal study with a miniature PET scanner (microPET, Concorde Microsystems, Knoxville, TN). Primary tumors mimicking the molecular mechanisms of human cancer were implanted in mice subcutaneously.

The MDA-MB-435 human breast carcinoma cell line was used to grow primary tumors in the study. During the period of tumor formation, dynamic FDG microPET images of the mice were acquired to monitor the tumor growth at early stage on a multiple-day base. Three mammary fat mice were used. In order to assure the early stage to be captured, different number of cells (10^6, $0.5x10^6$ and $0.1x10^6$) were injected into the same mouse under the two arms. In this means, the rates of tumor growth should be different.

Dynamic PET imaging of FDG (200 uci) was performed on a MicroPET R4 system (Concorde MicroSystems, Inc). Six days after inoculation, thirty-five dynamic data frames were acquired for 1 hr after intravenous injection – 6x1sec, 4x3 sec, 10x30 sec, 5x60 sec, and 10x300 sec. Images were reconstructed with the OSEM algorithm, as shown in Figure 2(a). The corresponding time-activity curves of the two tumors, normal tissues and heart have already been showed in Figure 2(b). The blood input function was measured in the images at a selected ROI in the heart area. Figure 2(c) is the transformed image of Figure 2(a) after passing through the constraint temporal filter.

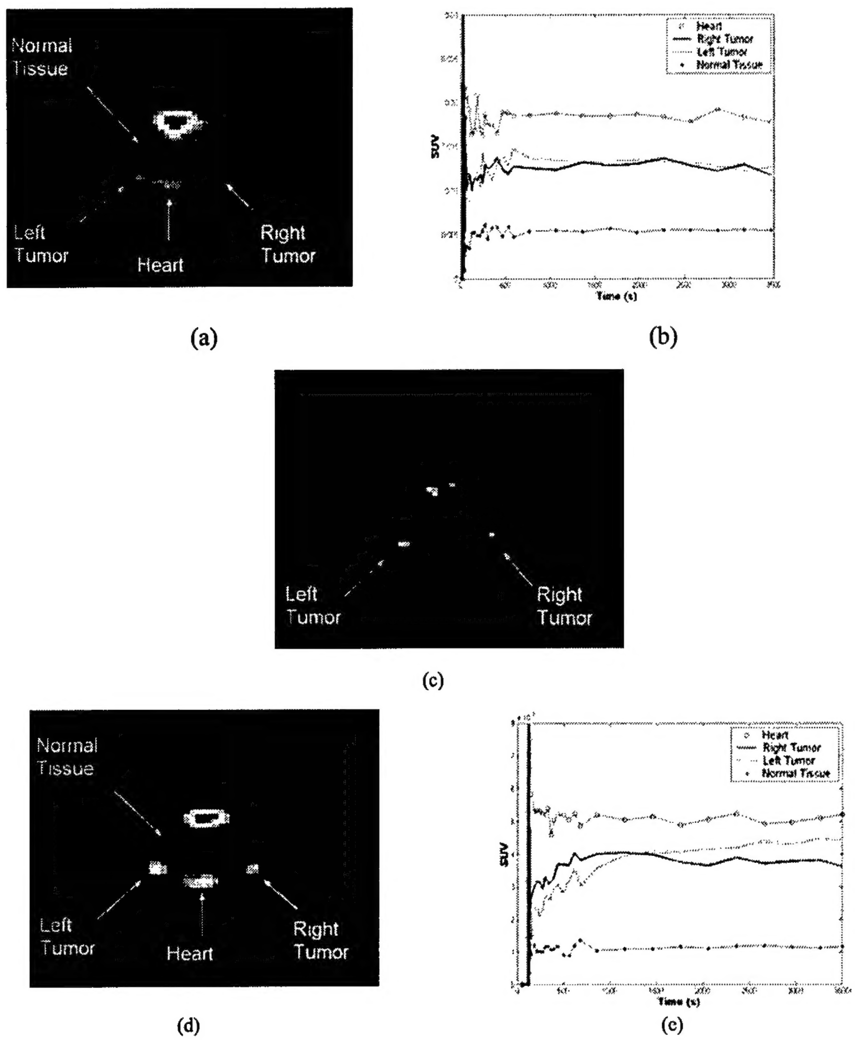


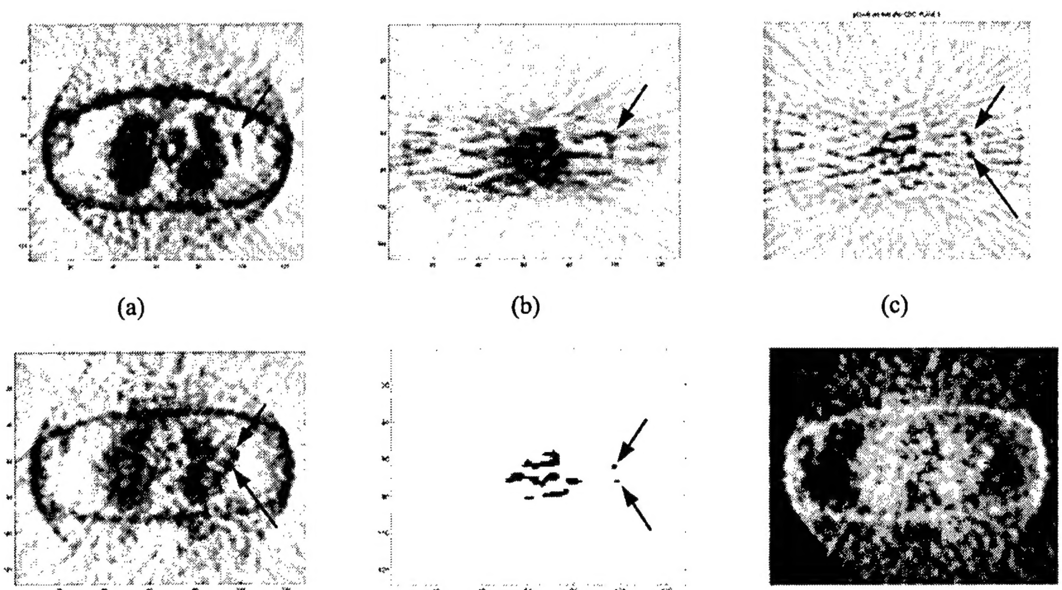
Fig. 2 Animal study: (a) Reconstructed FDG-PET image (6 days after inoculation). (b) TACs drawn from Fig. 2(a). (c) Transformed image of Fig. 2(a) by using constraint temporal filter. (d) Reconstructed FDG-PET image (12 days after inoculation). (e) TACs drawn from Fig. 2(d)

We also present another reconstructed image in Figure 2(d), which is acquired twelve days after inoculation. Figure 2(e) shows the corresponding TACs for the latterly acquired images. Comparing Figure 2(a) and Figure 2(b), it demonstrate that the tumors grow bigger and the slope of tumor's TAC becomes steep after six more days. Using these facts, we can confirm that the findings in the filtered output image shown in Figure 2(c) are correct.

2.3 Assessment of the developed methods patient data

Patient study

Case of breast cancer: Fig. 3 (a) shows an FBP image of a breast cancer data archive without attenuation correction, in which only one small axillary metastasis can be visualized, indicated by an arrow. Attenuation corrected version of the same slice is shown in Fig. 3 (b). Applying the primary tumor guided filtering, a method developed during this project, to the attenuation corrected dynamic images identified one extra metastasis as shown in Fig. 3 (c). These positive findings have been confirmed by a follow-up study acquired 1.5 years later (the patient had no interval treatment of her primary or metastatic disease). See Figure 3 (d). Between the two studies no treatment was given and the disease progressed. Applying a threshold to the filtered image in Figure 3 (c), the resulted detections are shown in Figure 3 (e). Overlaying the filtered image in red to the follow-up image, Figure 3 (f) demonstrates the computer identified metastases well aligned with those in the follow-up image. The slight misalignment between lesions and detections could be mitigated if an advancing registration accounting for non-rigid transformation was applied. Note that besides the two confirmed lesions, there are also some other pixels passing the threshold. This is because we only used a simple single pixel decision criterion. However, if we add the spatial size of lesions to be detected into the decision criterion, then we can get rid of the center parts in Figure 3(e). Moreover, the computer-generated likelihood of malignance will be reviewed by visual inspection. Combined with the additional knowledge of the patient's disease, the false positive findings in Figure 3 (e) can be eliminated.



(a) (b) (c)

(d) (e) (f)

Figure 3: (a) FBP image of a breast cancer without attenuation correction; (b) Attenuation correction of (a); (c) the filtered image of (b); (d) the follow-up image after 1.5 years; (e) the detection by the computer observer; (f) the image of overlaying (e) on (d).

Cases of lung cancer and inflammation : The developed spatial temporal filtering guided with the features extracted on a patient by patient base has also been applied to differentiate between malignancy and inflammation. Figure 6 shows a case of lung cancer and the corresponding filtering output image. Evidently the lesion was enhanced dramatically. As a contrast, Figure 5 presents a patient with lung cancer and joint inflammation where the joint is hot in the late frames of a dynamic PET scan. The simple, single template defined filter (mentioned in last annual report) was applied to process the data. We designed the filter using the physiological features extracted in a lung malignancy shown in Figure 4. In the filtered image, the "hot" spot caused by benign joint inflammation is filtered out the as normal tissue features. The result is shown in Fig. 5. This case demonstrates that the "hot" inflammation in FDGPET images may mislead visual inspection of static image, but with the feature guided spatial-temporal filtering, we can have a better chance to correctly distinct it from malignances.

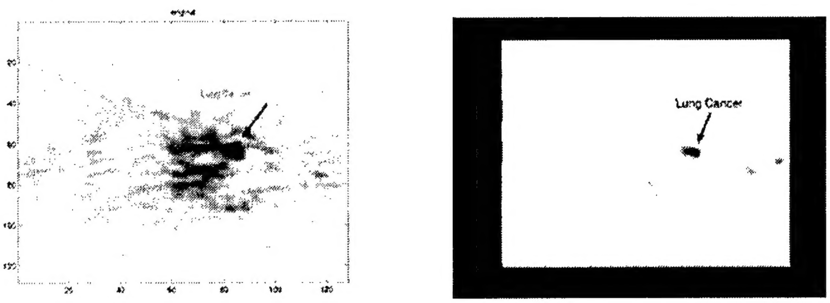
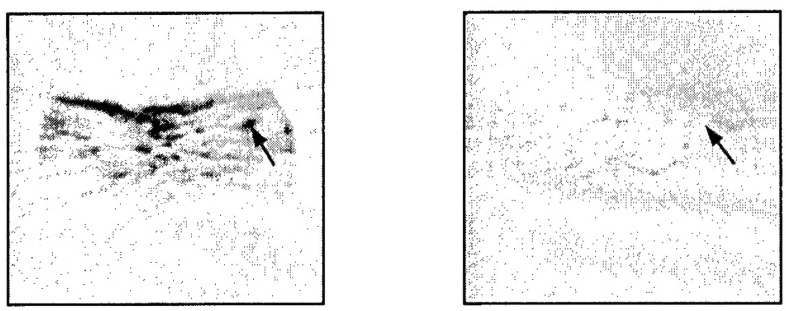


Figure 4: A lung lesion



(a) (b)

Fig. 5: (a) Joint inflammation in a patient with lung cancer, and (b) Filtered dynamic image of the same slice

3. Key Research Accomplishments

The main accomplishments in Year 4 (12 month no-cost extension) are

1. Assessment of accuracy of ROI-based molecular feature extraction with the real liver phantom data;

2. Development of the factor analysis aided feature extraction method to improve the accuracy of feature parameter estimation;

3. Assessment of non-invasive blood input function extraction with the patient data collected in clinical database at the USC PET center;

4. Design of space-temporal filtering criteria to identify metastases embedded from the unwanted noise and background interference;

5. Assessment of improving SNR via spatial-temporal filtering algorithms with the liver phantom data;

6. Establishment of patient data referrer relationship with the Division of Women's Imaging at the University of Southern California, which is composed of several modalities that work together or independently to diagnose women's health problems. These modalities include mammography, ultrasound (US), computerized tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and interventional procedures.

4. List of Reportable Outcomes:

4.1 -Publications

1. X. Yu, Z. Li, H. Jadvar and P. S. Conti, "Identification of Malignant and Benign Lesions in Dynamic PET Oncology", SNM Annual Conference 2003, New Orleans, San Louise, June 2003.

2. H. Jadvar, JR Bading and X Yu, PS Conti, "Dynamic FDG PET Kinetic Analysis of Inflammation and Cancer: Preliminary Results", SNM Annual Conference 2003, New Orleans, San Louise, June 2003.

3. J. Chen, X. Yu, "Enhanced Dynamic FDG-PET Tumor Detection with Constrained Temporal Filtering", Proceedings of IEEE International Conference on Medical Imaging, Portland, Or. October, 2003.

4. Z. Li, X. Yu, "Exploring Frequency Differences Of Physiological Processes To Enhance Dynamic FDG-PET", Proceedings of IEEE International Conference on Medical Imaging, Portland, Or. October, 2003.

5. J. Chen, X. Yu, "Rapid Assessment of PET Dynamic Images Using Computer Observers", submitted to IEEE International Symposium on Medical Imaging, November, 2003.

6. Z. Li, X. Yu, "Computer Aided Lesion Detection with Multi-channel Time-Frequency Analysis", submitted to IEEE International Symposium on Medical Imaging, November, 2003.

7. J. Chen, X. Yu, "Space-temporal Analysis and Processing of Dynamic PET Images", in preparation for submission to *J. of Med. Phy.*

8. Z. Li, X. Yu, "Frequency-time Analysis and Processing of Dynamic PET Images", in preparation for submission to *IEEE Trans. On Medical Imaging Processing*.

4.2 Graduation

Two students graduated with their M.S. degrees, respectively and became candidates of Ph. D. at the EE department, USC. Both were partially supported by this award.

5. Conclusion

The goal of this project is to improve detection of metastatic axillary breast cancer through sophisticated physiological modeling and statistical signal processing techniques. The major focus of Year 4 (no-cost extension) was to assessment of the developed methodology in feature identification, extraction/estimation, and early detection with digital phantom, animal study and a small amount of patient data. The methods we tested include (i) adding the factor analysis to the conventional ROI averaging method for feature extraction/estimation and (ii) to develop the optimal feature-guided filtering criteria for early lesion detection. The objective is to suppress the interference-plus-noise in dynamic data proceeding to applying the hypothesis test detection criteria. Two types of filters presented in the last annual report, with/without using the physiological features extracted from normal tissues, were further tested with digital phantom, animal study and patient data. The results of phantom study demonstrated that the accuracy of feature extraction in the modified method can be dramatically improved compared to the conventional ROI analysis and that the feature-guided space-temporal filters can enhance the SNR in invisible lesion and make it become detectable. The assessment of non-invasive blood time activity extraction was also performed with patient data selected from our clinical database. All findings in theory and simulations will be continued in the extended Year 5 when more clinical data will become available.

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